Remarks

In a response to a restriction requirement mailed to Applicants' Attorney on January 11, 2006. Applicants elected claims 1-3 and 12-13 (Group1) for further prosecution in this matter. As a result, claims 4-11 have been withdrawn and claims 1-3 and 12-13 remain pending. Applicants have furthermore previously amended claim 1 in a previous amendment and response dated March 28, 2007 by incorporating the limitations of claim 2 therein which is hereby cancelled. Applicants had also elected the chemical species (1-H-Benzoimidazol-2-yl)(2,6-dichlorophenyl) methyl amine hydrochloride (the species of example 2)

I. Claim Objection

The Examiner has objected to previously amended claim 1 due to an informality whereby in amended claim 1, under the definition of *R6 and R7,* "C_1 – C3 alkyl " was mis-spelled "alky". This has been corrected herein by amendment

II. Rejection under 35 U.S.C. § 112

The Examiner has rejected claims 1, 3, 12 and 13 under 35 U.S.C. §112(e) second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the present invention. It is asserted that in claim 1, since R6 and R7 no longer represent hydrogen as per the previous amendment to the first definition thereto of March 28, 2007, the proviso at the end of claim 1 which recites "provided that R6 and R7 are not hydrogen" no longer make sense. This confusion is certainly understood and has also been corrected herein by amendment as that proviso ay the end of claim 1 has been deleted for the purpose of clarity. The rejection of claims 1, 3 12 and 13 under 35 U.S.C. 102 (e) should respectfully therefore be withdrawn.

III. Rejection under U.S.C. 103(a)

The Examiner has continued to reject claims 1, 3, 12 and 13 as being unpatentable for obviousness under 35 U.S.C. §103(a) over Japanese Patent No. 02-306916 to Nishi et. al. taken together with WO 2002/46169 to Hofmeister et. al. (or its English counterpart, U.S. Patent No. 6,686,384), either considering both alone or in combination. It is asserted that whereas the present application at issue discloses and claims benzoimidazole compounds, both Nishi et. al. 306,916 and Hofmeister et. al. '384 teach benzoimidazole compounds which are structurally similar to those claimed herein.

It is furthermore asserted by the Examiner in support of her rejection for obviousness that the difference between the compounds of Nishi et al. and the compounds instantly claimed is that the instant claimed compounds are generically described in Nishi et al. However, it is also admitted that the difference between the compounds of Hofmeister et al. '384 and the compounds instantly claimed is that Hofmeister et al. discloses a secondary amine whereas the present invention comprises a tertiary amine as instantly claimed {i.e., -NH- in Hofmeister et al. versus –NR5- wherein R5 is alkyl as instantly claimed}.

The Examiner then argues that in order to make a prima facie case of obviousness, it is sufficient that the prior art reference compound merely be closely related to the claimed compound at issue to the extent that a chemist would find the difference between the two an obvious innovation. It is further asserted that in the case here, each of Nishi et. al. and Hofmeister et al. '384 teach benzoimidazole compounds that are structurally similar to each other and to those of the present claimed invention and are therefore useful in treating some of the same diseases/disorders. Hence, the Examiner reasons that the combination of Nishi et. al. '916 and Hofmeister et. al. '384 would teach the instant claimed invention. The pharmaceutical compounds and compositions of the present invention would have been suggested by the references to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art under 35 U.S.C. §103(a). This rejection is also respectfully traversed for the following reasons.

The Examiner has respectfully erred in her determination that the compounds disclosed in Nishi et. al. '916 and Hofmeister et. al. '384 are structurally similar to those claimed herein and therefore will be useful in the treatment of the same diseased states, thereby rendering the present claimed invention obvious. In light of the fact the Examiner has essentially repeated her rejection for obviousness under §103 set forth in the office action of 2/1/07, Applicants must again respond by reiterating that it is well established that structural similarity between chemical compounds alone **is not** sufficient to establish obviousness.

Chemical compounds present special issues of obviousness because of the limited number of elements, the existence of recurring groups or substitutes in complex molecules, the structural similarities within classes of related compounds, and the ability of chemists to undertake systematic experiments modifying known compounds. As a result, even if structural similarity may exist between the claimed and prior art subject matter, one must still show that the prior art suggests a reason or motivation to make the claimed compositions

Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc. 471 F.3d 1369, 81 U.S.P.Q. 2d 1324 (Fed. Cir. 2006) citing In re May and Eddy 574 F.2d 1082, 197 U.S.P.Q. 601 (C.C.P.A. 1978)

For it is well established that chemistry is a highly empirical science and as such the art is unpredictable. Therefore there is no valid presumption that structurally similar claimed and prior art compounds have similar properties or will react with other compounds in the same way. *In re May*, supra., In re Papesch, 315 F.2d 381, 50 CCPA 1084, 137 USPQ 43 (C.C.P.A.1963).

Therefore, there is no expectation that structurally similar compounds will possess similar therapeutic activity. It is well known in the art that the mere change or substitution of one of the moieties on the molecule of a chemical compound can completely change its' physico-chemical properties. Moreover, it

is well established in the case law that chemistry and chemical compounds are, by their nature very unpredictable in the manner in which the will react. Neither of the cited references, taken either alone or in combination, disclose or even suggest the claimed compounds of the present invention. Japanese Patent Application No. 02-306916 to Nishi et al. is directed to certain benzothiazoles and benzoimidazoles, which are disclosed as being useful as blood platelet adhesion inhibitors. Nishi et al. does not disclose any (benzoimidazol-2yl)-phenylamine compounds which are substituted in one or both of the ortho-positions of the phenyl ring as required in the claimed compounds of the present invention. For example, in the claimed compounds of the present invention, substituents R6 and R7 cannot be hydrogen which are a necessary component of the compounds disclosed in the Nishi et. al reference.

Examiner Stockton has also cited the disclosure of a "2, 6-dichlorophenyl" compound in the first full paragraph on page 12 in the English translation of Nishi et al., to show that the cited reference teaches benzoimidazol-2yl)-phenylamine compounds which are substituted in one or both ortho-positions of the phenyl ring. However, this paragraph discloses a very large number of examples of substituted phenyl groups. Substituted phenyl groups are widely used in the definitions of various substituents in the generic compounds described in Nishi et. al. The paragraph may teach a **very large** genus of these compounds, but it does not however, teach or suggest any of the specifically claimed structures disclosed and claimed in the present application. Moreover, it certainly does not suggest the claimed compound that comprises an optional variant moiety R10 or R11 (when R2 is defined as –NR10R11). Nor does the cited paragraph teach or disclose how the disclosed generic structure of Nishi corresponds to the phenyl ring in the claimed (benzoimidazol-2yl)-phenylamine compounds of the present invention.

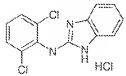
Furthermore, the list of examples for substituted phenyl group comprises about 50 examples, but only one example with a 2,6-substitution. Additionally,

not a single exemplified compound is disclosed in Nishi et al., in which the phenyl ring of the (benzoimidazol-2yl)-phenylamine is substituted in one or both of the ortho-positions. And, considered as a whole, the Nishi et. al. patent discloses literally **hundreds** of possible compounds out of which a genus of compounds related to those claimed herein might be selectively sought out and revealed. Therefore, notwithstanding the Examiners' assertions to the contrary, Nishi et al. does not teach any compounds which might render obvious those recited in the claims at issue.

On top of this distinction, the claimed compounds of the present invention cannot be substituted in the meta- or para- position of the phenyl ring as disclosed by the compound in example 23 of Nishi et. al. cited by the Examiner. Nishi et al. does not suggest the use of the claimed compounds as NHE-3 inhibitors for the treatment or prophylaxis of a disorder of the respiratory system, sleep-related respiratory disorders, sleep apneas or snoring. Therefore, the compounds of the present invention as claimed are not obvious in view of Nishi et al.

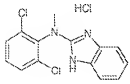
Hofmeister et al. '384 is directed to phenylamino-substituted benzoimidazols wherein the amino-group can only be substituted with hydrogen in addition to the phenyl substituent R5 on the amino group. With respect to this structure, a person skilled in the art would expect a lower solubility of these resulting compounds due to the additional lipophilic substituent. The following comparative experiment shows that the solubility – in contrast to what a person skilled in the art would have expected – is higher for the compounds of formula I than for the compounds according to Hofmeister et al.:

Hofmeister et. al. '384 (WO 0246169)



IC50(NHE3) = 53 μm; solubility (**6.25 μM**; PBS buffer) see example 1 of WO 0246169 and U.S. Patent 6,686,384 to Hofmeister et. al.

However, example 2 of the present application shows data for a compound of the present invention as follows:



IC50(NHE-3) = 53 μm; solubility (**150 μM**; PBS buffer).

Not only are the compounds' structures different, but their solubilities dramatically so. Hence, Hofmeister et. al fails to suggest those compounds recited in the amended claims at issue and/or their respective properties and utilities

Despite the Examiners' continued rejection whereby she does not give full weight and measure to the importance of the distinction regarding the difference in the prior art compounds' and the present claimed compounds' solubilities, the dramatic difference therein is important in terms of a finding of non-obviousness since solubility is an important factor in the use of these claimed compounds as pharmaceuticals. Hence, for one skilled in the art of medicinal chemistry, it is clear that a higher solubility is very important. See page 617 (last paragraph) – p. 618 (first paragraph) of The Practice of Medicinal Chemistry, (Elsevier Press, 2nd edition; 2003) wherein it is stated:

Chemically solubilized active principles render possible the preparation of parenteral and especially intravenous forms appreciated in clinical practice..... and the use of water-soluble molecules is recommended as they are therapeutically more effectively.

And even if one were to conclude the references *were* combinable so as to support an argument of obviousness (for which it is submitted there is no inherent motivation to do) the claimed compounds of the present invention with their

exhibited surprising and unexpected properties would clearly not be evident and therefore cannot be regarded as obvious. For it is also well founded that in order to establish a prima facie case of obviousness under 35 U.S.C. §103 it is not sufficient to merely identify each element from the claimed invention in the prior art. A party alleging invalidity due to obviousness must articulate the reasons why one of ordinary skill in the art would have been motivated to select the references and combine them so as to arrive at the claimed invention at issue *Abbott Laboratories v. Andrex Pharmaceuticals Inc.* 452 F3d 1331, 1336; 69 U.S.P.Q. 2d 597 (Fed. Cir, 2006) *sanofi-synthelabo Inc. v. Apotex Inc.* 470 F3d 1368, 1379; 81 U.S.P.Q. 2d 1097 (Fed Cir. 2007) Whereas the teaching, suggestion or motivation ("TSM") to combine the references may not necessarily need to be found within the cited prior art references themselves, and it is now recognized that there is flexibility in our obviousness jurisprudence because a motivation may be found *implicitly* in the prior art. *KSR Inc., V Teleflex Inc.*127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385 (2007). And whereas the *KSR* case was one concerned with the more predictable mechanical/electrical arts, the Court affirmed that a test for obviousness must be applied on a case-by-case basis and that more unpredictable ares of science such as pharmaceuticals and chemistry could not be analyzed in the same way. Said "TSM" must still exist or be within the general knowledge of one skilled in the art and said TSM must give the skilled artesian a reasonable expectation of success in doing so. *Pfizer Inc. v. Apotex Inc.* 2006-1261 (Fed. Cir 2006). There is no such reasonable expection here due to the unpredictable nature of the pharmaceutical/chemical arts..

It is also well established that "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir 2006) Here clearly, there is no such reasoning given. Nishi et. al. fails to teach or disclose any (benzoimidazol-2yl)-phenylamine compounds which are substituted in one or both of the ortho-positions of the phenyl ring as required in the claimed compounds of the present invention. And the allegedly "generically similar" compounds (as

described by the Examiner) disclosed therein must be chosen from a group of hundreds of otherwise totally unrelated compounds. This is not the mandated reasoning that supports a rational conclusion of obviousness.

Moreover, with respect to the claimed compounds herein, substituents R6 and R7 cannot be hydrogen which **is** the case in the Nishi et. al reference. Therefore, this does not suggest or teach the benzoimidazol phenylamine compounds with the substituted groups as disclosed herein nor does Hofmeister et al '384 provide any such teaching or motivation to do so since Hofmeister et al. '384 is directed to phenylamino-substituted benzoimidazols wherein the amino-group can only be substituted with hydrogen in addition to the phenyl substituent R5 on the amino group. One cannot combine the teachings of Hofmeister et. al. with that of Nishi so as to come up with the claimed compounds of the present invention since they in fact teach away therefrom due to the non-interchangeability of the molecular substituents, i.e., it is impossible to make some substituent changes on Nishis' compounds knowing Hofmeister et. al. in order to come up with the claimed compounds of the present invention since R6 and R7 cannot be hydrogen. Therefore, the rejection of claims 1, 3,12 and 13 for obviousness under 35 U.S.C. §103 must respectfully be withdrawn.

Applicants respectfully submit that it is improper to pick out isolated features in earlier prior art patents, combine them in one particular way with application of hindsight acquired only from the Applicant's own disclosure, and then say that it would have been obvious to select those particular features and to combine them in the particular way in which the Applicant has. *Eversharp, Inc. v. Fisher Pen Co.*, 204 F. Supp. 649, 662-63, 132 U.S.P.Q. 423, 434 (N.D. Ill.
1961). There must be some teaching or suggestion in the references to support their use in the particular claimed combination. A retrospective view of inherency is not a substitute for some teaching or suggestion, which supports the selection and use of the various elements in the particular claimed combination. Care must be taken to avoid hindsight reconstruction by using the Applicant's own disclosure as a guide through the maze of prior art references, combining the

right references in the right way so as to achieve the result an Applicant claims *Grain Processing Corp. v. American Maize Prods.*, 840 F.2d 902, 907, 5 U.S.P.Q. 2d 1788, 1792 (Fed. Cir. 1988); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012, 217 U.S.P.Q. 193, 199 (Fed. Cir.1983).

In conclusion, it is insufficient for the Examiner to merely show that each separate element of a claimed compound can be found in two separate prior art references. The mere fact that it is possible to find a generic disclosure of a compound buried in a plethora or laundry list of compounds from two isolated disclosures does not necessarily render such selection and construction obvious unless the knowledge of one skilled art also contains something to motivate or suggest the desirability of the proposed combination. It is wrong to use the patent in suit as a guide through the maze of prior art compounds disclosed in two references and using this combine them in just the right way so as to achieve the result of the claims in suit, as Monday morning quarterbacking is quite improper when resolving the question of non-obviousness in a court of law.

In light of the foregoing amendments to the claims and arguments as to their patentability, it is respectfully asserted that the remaining pending claims recite patentable subject matter that is clearly distinguishable and an advance over the cited prior art. It is further respectfully requested that said rejections of the claims be withdrawn so that they might pass to allowance and issue. Should however, the Examiner still have some remaining issue(s) or concern(s), he is earnestly solicited to contact the undersigned attorney so that the un-resolved matter might be overcome and resolved.

Respectfully submitted,

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